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09/600,714	10/04/2000	Willy A. Flegel	12086-002001	9364

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EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	15

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/600,714	FLEGEL ET AL.	
	Examiner	Art Unit	
	" Neon" Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover she t with th correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-51* is/are pending in the application.

4a) Of the above claim(s) *13 and 15-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12, 14 and 48-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-51 are pending.

2. Claims 13, 15-47 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. In view of the amendment filed 3/8/02, the following objection and rejections remain.

4. The disclosure stands objected to because of the following informality: (1) the arrangement of the specification. See Arrangement of the Specification in Action mailed 9/25/01. Appropriate correction is required.

5. The drawings, filed 10/4/00, stand not approved.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-12, 14 and 48-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a nucleic acid molecule comprising SEQ ID NO: 41 encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying at least one missense mutation, as compared to the wild type Rhesus D antigen, in its transmembrane and/or intracellular regions for screening missense mutation in *RHD* gene, (2) a nucleic acid molecule comprising SEQ ID NO: 41 encoding a human Rhesus D antigen that contributing to or indicative of the weak D phenotype, said nucleic acid molecule a) carrying at least one missense mutation, as compared to the wild type Rhesus D antigen, in amino acid positions such as the ones recited in claim 4, (b) carrying a gene conversion involving exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene, (3) the said nucleic acid molecule wherein said missense mutation occurs in the nucleotide position such as the ones recites in claims 5, 6 and 8, (4) the said nucleic acid molecule wherein said combination of amino acid substitution in the positions such as the ones recited in claims 7

and 49, (5) the said nucleic acid molecule wherein said combination of missense mutations consisting of positions such as the ones recited in claim 8, (6) a vector comprising the nucleic acid molecules mentioned above, (7) a host cell transformed with said vector, (8) a method of producing a Rhesus D antigen contributing to the weak D phenotype comprising culturing said host cell under suitable conditions and isolating the Rhesus D antigen produced, (9) an oligonucleotide selected from the group consisting of SEQ ID NOS: 3-4, 7, 16-18, 20, 23, 25-26, 29-30 and 39-40 hybridizing under 0.1X SSC, 0.1% SDS at 65°C hybridization and washing conditions to a portion of the nucleic acid molecule mentioned above comprising said at least one missense mutations or to the complementary portion thereof or hybridizing to a region involving the breakpoint of the gene conversion identified in claim 2 for screening missense mutation in *RHD* gene, **does not** reasonably provide enablement for (1) *any* nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying at least one missense mutation, as compared to the wild type Rhesus D antigen, in its transmembrane and/or intracellular regions for screening missense mutation in *RHD* gene, (2) *any* nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule a) carrying at least one missense mutation, as compared to the wild type Rhesus D antigen, in *any* amino acid positions such as 2-16, 114-149, 179-225, and/or 267 to 397, (3) *any* nucleic acid molecule mentioned above wherein said missense mutation causes *any* amino acid substitution in position 3, 10, 16, 114, 149, 182, 198, 201, 220, 223, 270, 276, 277, 282, 294, 295, 307, 339, 385 or 393 or any combination of said substitution, (4) *any* nucleic acid molecule mentioned above wherein said missense mutation is *any* base pair substitution occurs in nucleotide position such as the ones recited in claim 5, (5) *any* nucleic acid molecule mentioned above wherein said molecule is *any* mRNA or *any* genomic DNA, (6) *any* vector comprising *any* nucleic acid molecule mentioned above, (7) *any* host cell transformed with *any* vector mentioned above, (8) a method of producing *any* Rhesus D antigen contributing to the weak D phenotype comprising culturing said host cell under suitable conditions and isolating the Rhesus D antigen produced, (9) *any* oligonucleotides hybridizing under 0.1X SSC, 0.1% SDS at 65°C to any portion of any nucleic acid molecule of any one of claims 1 or comprising at least one missense mutation or to the complementary portion thereof or hybridizing to any region involving the breakpoint of the gene conversion identified in claim 2, (10) *any* kit comprising *any* oligonucleotide mentioned above, and (11) *any* oligonucleotide 12 to 50 or 15 to 24 nucleotides in length. The specification does not enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims for the same reasons set forth in Paper No 12.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only one polynucleotide of SEQ ID NO: 41 that encodes a human Rhesus D antigen carrying one or more missense mutations which contribute to weak D phenotype and the specific missense mutations in the polynucleotide of SEQ ID NO: 41 occurs in nucleotide position 8 is from C to G, in position 29 from G to A, in position 48 from G to C, in position 340 from C to T, in position 446 from C to A, in position 544 from T to A, in position 594 from A to T, in position 602 from C to G, in position 658 from T to C, in position 667 from T to G, in position 809 from T to G, in position from 819 from G to A, in position 826 from G to C, in position 830 from G to A, in position 845 from G to A, in position 880 from G to C, in position 885 from G to T, in position 919 from G to A, in position 1016 from G to A, in position 1154 from G to C, and in position 1177 from T to C, or in a combination of said position. The specification further discloses a nucleic acid molecule encoding a human Rhesus D antigen contributing to the weak D phenotype carrying at least one missense mutation, as compared to the wild type Rhesus D antigen wherein the missense mutation causes an amino acid substitution in position 3 from Ser to Cys, in position 10 from Arg to Gln, in position 16 from Trp to Cys, in position 114 from Arg to Trp, in position 149 from Ala to Asp, in position 182 from Ser to Thr, in position 198 from Lys to Asn, in position 201 from Thr to Arg, in position 220 from Trp to Arg, in position 223 from Phe to Val, in position 270 from Val to Gly, in position 276 from Ala to Pro, in position 277 from Gly to Glu, in position 295 from Met to Ile, in position 307 from Gly to Arg, in position 339 from Gly to Glu, in position 385 from Gly to Ala, in position 373 from Trp to Arg or in a combination of said position for screening assays. Finally, the specification discloses the specific oligonucleotides of SEQ ID NOS: 3-4, 7, 16-18, 20, 23, 25-26, 29-30 and 39-40 as

shown in Table 1 on page 33 that are *RHD* specific for screening missense mutation in *RHD* gene.

With the exception of the specific nucleic acid molecule of SEQ ID NO: 41 carrying the missense mutation at the specific base pair or amino acid residues and the specific oligonucleotides mentioned above, the specification does not teach how to make and use *any* "nucleic acid molecule" that would encode a human Rhesus D antigen which contribute to a weak D phenotype as a consequence of missense mutation because there is no structure and function associated with said "nucleic acid molecule" without a SEQ ID NO. By reciting just the "nucleic acid molecule" in the preamble without the SEQ ID NO in claims 1 and 2, the said "nucleic acid molecule" can encompass an infinite number of polynucleotide that may or may not encode a Rhesus D antigen, let alone carrying missense mutation in various nucleotide and, amino acids position. Given the indefinite number of "nucleic acid molecule", there is insufficient guidance in the specification as to which position within the full length of the undisclosed "nucleic acid molecule" that after substitution, deletion or insertion will retain both structure and function similar to SEQ ID NO: 41 such as contributing to or indicative of weak D phenotype. As such, it is unpredictable to determine which undisclosed "nucleic acid molecule" would be useful for screening the presence of one or more missense mutation in Rh D antigens of blood of donor and recipient. Since the specification fails to provide guidance regarding which nucleotide within the undisclosed "nucleic acid molecule" can tolerate change, it follows that the amino acid encoding by the undisclosed "nucleic acid molecule" is not enable. It also follows that any undisclosed nucleic acid molecule encoding a human Rhesus D antigen wherein said nucleic acid molecule carrying at least one missense mutation in any amino acid positions such as the ones recited in claims 2a, 3, 4 and 7 is not enabled. It follows that any undisclosed nucleic acid molecule encoding a human Rhesus D antigen wherein said nucleic acid molecule carrying a gene conversion involving exons 6 to 9 which are replaced by the corresponding exons of any undisclosed RHCE gene is not enable. It also follows that any undisclosed nucleic acid molecule encoding a human Rhesus D antigen wherein said nucleic acid molecule carrying at least one missense mutation occurs in nucleotide position such as the ones recited in claim 5, 6, and 8 are not enable. Because of the indefinite number of undisclosed "nucleic acid molecule" encompassed by the claims, the vector comprising any undisclosed "nucleic acid molecule" as recited in claim 10 is not enabled. Since the vector comprising said "nucleic acid molecule" is not enabled, any host cells to be transformed with said vector and the method of producing a

Rhesus D antigen that contributes to the weak D phenotype as recited in claims 11-12 are not enabled.

With regard to "oligonucleotide", the claim encompasses any random sequence of 12 to 50 or 15 to 24 nucleotides in length. There is insufficient guidance and working examples in the specification that any random oligonucleotide (without the specific nucleotide sequence such as SEQ ID NO) as long as it is 12 to 50 or 15 to 24 nucleotide in length would even hybridize under the condition such as 0.1X SSC, 0.1% SDS at 65°C to any undisclosed nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype. Even if the nucleic molecule encoding a human Rhesus D antigen is disclosed, without the specific nucleotide sequence in the oligonucleotide, it is unpredictable which undisclosed oligonucleotide would bind specifically to said nucleic molecule encoding a human Rhesus D antigen. Given the indefinite numbers of oligonucleotides, the lack of guidance and insufficient number of working examples, it is unpredictable to determine which undisclosed oligonucleotides would hybridize specifically to the undisclosed "nucleic acid molecule" that encodes a human Rhesus D antigen, in turn, would be useful for screening the presence of one or more missense mutation in Rh D antigens of blood of donor and recipient that contribute to the weak D phenotype.

The state of the prior art as exemplified by Wallace *et al* and Sambrook *et al* is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. Even if the probe is a 20mer, the total number of hits in a database search was 143,797,728, which suggest that some of the probes encompassed by the claims would not preferentially hybridize to a "nucleic acid molecule" that encodes a Rhesus D antigen. Since the undisclosed oligonucleotide would not hybridize specifically to the "nucleic acid molecule" that encodes a Rhesus D antigen, it follows that the oligonucleotide would not specifically hybridize to the "complementary portion thereof" or any region involving the breakpoint of the gene conversion as recited in claim 14. It follows that any kit comprising said "oligonucleotide" is not enable.

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention without undue amount of experimentation. As such, further research would be required to practice the claimed invention.

Applicants' arguments filed 3/8/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) claims 1 and 2 have been amended to recite that the nucleotide molecule encodes "human" Rhesus D antigen contributing to or indicative of a weak D phenotype, (2) the specification exemplifies 22 different nucleic acid molecules that encode a human Rhesus D antigen contributing to or indicative of a weak D phenotype, (3) the nucleotide sequences of other human RHD alleles can be easily identified using routine molecular biology, (4) the human RHD alleles are highly conserved among human individuals, (5) nucleic acids that do not encode Rhesus D antigen are not included in claims 1 and 2, (6) the specification exemplifies missense mutations that contribute to or are indicative of the weak D phenotype such as the ones discloses on page 8, lines 5-12, and such missense mutations are within either the transmembrane or intracellular region of Rhesus D antigen on page 6, lines 15-18; the specification also discloses a gene conversion indicative of weak D phenotype, exons 6 to 9 replaced with the corresponding exons of RHCE (page 6, lines 13-14), (7) claim 14 has been amended to recite particular hybridization conditions, the claimed oligonucleotides would preferentially hybridize to a portion of the nucleic acid of claims 1 or 2 comprising at least one missense mutation or complementary portion thereof or hybridizing to a region involving the breakpoint of the gene conversion of claim 2.

However, the amended claims 1 and 2 still do not recite a specific SEQ ID NO. Without the SEQ ID NO in the claims, there is no structure/function associated with "A nucleic acid molecule". Although applicants have amended claim 14 to recite the specific hybridizing condition, and added claims 50 and 51 to recite the specific length to the "oligonucleotide", it is insufficient to overcome this rejection because there is no structure (SEQ ID NO) that defines the specific oligonucleotide sequence that would hybridize specifically to nucleic acid molecule that encodes a human Rhesus D antigen under the specified condition.

8. Claims 1-12, 14 and 48-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying at least one missense mutation, as compared to the wild type Rhesus D antigen, in its transmembrane and/or intracellular regions for screening

missense mutation in *RHD* gene, (2) *any* nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule a) carrying at least one missense mutation, as compared to the wild type Rhesus D antigen, in *any* amino acid positions such as 2-16, 114-149, 179-225, and/or 267 to 397, (3) *any* nucleic acid molecule mentioned above wherein said missense mutation causes *any* amino acid substitution in position 3, 10, 16, 114, 149, 182, 198, 201, 220, 223, 270, 276, 277, 282, 294, 295, 307, 339, 385 or 393 or any combination of said substitution, (4) *any* nucleic acid molecule mentioned above wherein said missense mutation is *any* base pair substitution occurs in nucleotide position such as the ones recited in claim 5, (5) *any* nucleic acid molecule mentioned above wherein said molecule is *any* mRNA or *any* genomic DNA, (6) *any* vector comprising *any* nucleic acid molecule mentioned above, (7) *any* host cell transformed with *any* vector mentioned above, (8) a method of producing *any* Rhesus D antigen contributing to the weak D phenotype comprising culturing said host cell under suitable conditions and isolating the Rhesus D antigen produced, (9) *any* oligonucleotides hybridizing under 0.1X SSC, 0.1% SDS at 65°C to any portion of *any* nucleic acid molecule of any one of claims 1 or comprising at least one missense mutation or to the complementary portion thereof or hybridizing to any region involving the breakpoint of the gene conversion identified in claim 2, (10) *any* kit comprising *any* oligonucleotide mentioned above, and (11) *any* oligonucleotide 12 to 50 or 15 to 24 nucleotides in length.

With the exception of the specific nucleic acid molecule of SEQ ID NO: 41 encoding a human Rhesus D antigen carrying the missense mutation at the specific nucleotide or amino acid residues and the specific oligonucleotides mentioned above, there is no description about the structure associated with any "nucleic acid molecule" mentioned above, that is critical for screening blood of donor and recipient for the presence of one or more missense mutation in the Rh D antigen. Given that the "nucleic acid molecule" is not adequately described, the complementary thereof and any region involving the breakpoint of the gene conversion are not adequately described for the same reasons as mentioned above. It is noted that though the claimed invention is directed to "nucleic acid molecule", the principle still holds for the amino acid encoded by said "nucleic acid molecule". Sine only one polynucleotide of SEQ ID NO: 41 that encodes a Rhesus D antigen is disclosed, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus.

With the exception of oligonucleotides of SEQ ID NOS: 3-4, 7, 16-18, 20, 23, 25-26, 29-30 and 39-40, there is insufficient written description about the structure associated with *any*

"oligonucleotide" because the specific nucleotides are not described. Given the indefinite number of oligonucleotide that may encompassed by the claim, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 3/8/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) claims 1 and 2 have been amended to recite that the nucleotide molecule encodes "human" Rhesus D antigen contributing to or indicative of a weak D phenotype, (2) the specification exemplifies 22 different nucleic acid molecules that encode a human Rhesus D antigen contributing to or indicative of a weak D phenotype, (3) the nucleotide sequences of other human RHD alleles can be easily identified using routine molecular biology, (4) the human RHD alleles are highly conserved among human individuals, (5) nucleic acids that do not encode Rhesus D antigen are not included in claims 1 and 2, (6) the specification exemplifies missense mutations that contribute to or are indicative of the weak D phenotype such as the ones discloses on page 8, lines 5-12, and such missense mutations are within either the transmembrane or intracellular region of Rhesus D antigen on page 6, lines 15-18; the specification also discloses a gene conversion indicative of weak D phenotype, exons 6 to 9 replaced with the corresponding exons of RHCE (page 6, lines 13-14), (7) claim 14 has been amended to recite particular hybridization conditions, the claimed oligonucleotides would preferentially hybridize to a portion of the nucleic acid of claims 1 or 2 comprising at least one missense mutation or complementary portion thereof or hybridizing to a region involving the breakpoint of the gene conversion of claim 2.

However, the amended claims 1 and 2 still do not recite SEQ ID NO: 41. Without the SEQ ID NO in the claims, there is no structure/function associated with "A nucleic acid molecule". Although applicants have amended claim 14 to recite the specific hybridizing condition, and added claims 50 and 51 to recite the specific length to the "oligonucleotide", it is insufficient to overcome this rejection because there is no structure (SEQ ID NO) that defines the

specific nucleotide sequence that would hybridize specifically to nucleic acid molecule that encode a human Rhesus D antigen.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. It is noted that the reference cited by the Examiner, LeVan et al, (of record, Blood 83: 3098-3100, 1994; PTO 892), is incorrect. The correct citation is Westhoff *et al,* (of record, Blood 83: 3098-3100, 1994; PTO 892).

11. Claims 1, 2, 9, and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Westhoff *et al* (of record, Blood 83: 3098-3100, 1994; PTO 892).

Westhoff *et al* teach a polynucleotide (Accession number A46368) that encodes a human Rhesus D antigen (isolated from human K562 cells) carrying one missense mutation at the amino acid position 218 which is within the amino acid position from 114 to 149 as recited in instant claim 2 and does not carry a single missense mutation leading to a substitution of phenylalanine in amino acid position 223 by valine or threonine in position 283 by isoleucine (See enclosed sequence alignment, in particular). Claim 9 is include in this rejection because the reference polynucleotide is genomic DNA. Westhoff *et al* further teach PCR primers, which are oligonucleotides that hybridize under stringent conditions to the reference polynucleotide carrying missense mutation or the complementary thereof (See page 3098, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 3/8/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) Westhoff *et al* do not describe a missense mutation, which results in a Met residue at position 218, and (2) the enclosed Cartron et al (Transfus. Clin. Biol. 6: 497, 1996, Exhibit B) indicate that a previously described RHD gene sequence with Ile at position 218 resulted from a sequence error, which cited Kim et al in Proc. Natl. Acad. Sci UDA 89: 10925, 1992.

However, the Exhibit B describes a different reference than the one cited by the Examiner, and the reference cited is Westhoff *et al* (of record, Blood 83: 3098-3100, 1994).

Further, applicants are claiming any nucleic acid sequence encoding a human Rhesus D antigen, not just the specific nucleic acid molecule of SEQ ID NO: 41 having a missense mutation in its transmembrane and/or intracellular regions.

12. Claims 1-4, 9 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Cherif-Zahar *et al* (of record, Proc. Natl. Sci. U.S.A. 87: 6243-6247, 1990; PTO 892).

Cherif-Zahar *et al* teach a polynucleotide (Accession number A30405) that encodes a Rhesus D antigen carrying at least one missense mutation (See enclosed sequence alignment, in particular). The reference polynucleotide carries a missense mutation at the amino acid position range from 179-225 as recited in instant claim 2 and does not carry a single missense mutation leading to a substitution of phenylalanine in amino acid position 223 by valine or threonine in position 283 by isoleucine (See enclosed sequence alignment, in particular). The missense mutation in the reference polynucleotide causes by an amino acid substitution at position at 182, 198 and 223 as recited in instant claim 3 (See enclosed sequence alignment, in particular).

The missense mutation in the reference polynucleotide causes by an amino acid substitution at position 182 to Thr, at position 198 to Asn, at position Val as recited in instant claim 4 (See enclosed sequence alignment, in particular). Claim 9 is include in this rejection because the reference polynucleotide is genomic DNA (See page 6243, Materials and Methods, in particular). Cherif-Zahar *et al* further teach oligonucleotides (primers) that hybridize to the reference polynucleotide or a portion thereof and the complementary thereof carrying missense mutation (See page 6243, Materials and Methods, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 3/8/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) Cherif-Zahar *et al* do not describe a nucleic acid molecule encoding a human Rhesus D antigen as required by amended claims 1 and 2 and (2) the accession number A30405 is an RHCE sequence.

However, the reference sequence was isolated from human (See abstract, in particular). With regard to cited reference is an RHCE sequence, the reference sequence appears to be the same as the claimed nucleic acid molecule. Since the Patent Office does not have the facilities for examining and comparing the nucleic acid molecule of the instant invention to those of the prior art, the burden is on applicant to show a side by side comparison that the prior art sequence

is different from the claimed nucleic acid molecule. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Thus, the reference teachings anticipate the claimed invention.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 10-12, 14 and 50-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Westhoff *et al* (of record, Blood 83: 3098-3100, 1994; PTO 892) or Cherif-Zahar *et al* (of record, Proc. Natl. Sci. U.S.A. 87: 6243-6247, 1990; PTO 892) each in view of Sambrook *et al* (*Molecular Cloning*, 1989, Cold Spring Harbor Laboratory, CSH, NY, Ch. 17).

The teachings of Westhoff *et al* and Cherif-Zahar *et al* have been discussed supra.

The claimed invention in claim 10 differs from the references only by the recitation of a vector comprising the nucleic acid encoding Rhesus D antigen.

The claimed invention in claim 11 differs from the references only by the recitation of a non-human host cell transformed with the vector of claim 10.

The claimed invention in claim 12 differs from the references only by the recitation of a method of producing a Rhesus D antigen contributing to the weak D phenotype comprising culturing a host cell of claim 11 under suitable conditions and isolating the Rhesus D antigen.

The claimed invention in claim 14 differs from the references only by the recitation of an oligonucleotide hybridizing under stringent conditions to a portion of the nucleic acid molecule of any one of claims 1 to 9 comprising said at least one missense mutation or to the complementary

portion thereof or hybridizing to a region involving the breakpoint of the gene conversion identified in claim 2.

The claimed invention in claim 50 differs from the references only by the recitation that the oligonucleotide is 12 to 50 nucleotides in length.

The claimed invention in claim 51 differs from the references only by the recitation that the oligonucleotide is 15 to 24 nucleotides in length.

Sambrook *et al* teach cloning a cDNA into an expression vector, a process of transforming the expression vector into host cells, culturing the host cells under conditions in which the polypeptide is expressed and then recovering the polypeptide from the culture. Sambrook *et al* teach that it is desirable to use recombinant DNA techniques for the production of biologically active proteins in order to produce proteins of higher concentration and purity. Sambrook *et al* further teaches how to make and use oligonucleotide probes that hybridize to any polynucleotide and guidelines for selection of conditions that promote maximal specificity of hybridization for screening and rapid isolation of cloned copies of genes (See chapter 11, in particular). Sambrook *et al* teach oligonucleotide such as 19-40 nucleotides are sufficiently long to allow the use of hybridization conditions that can guarantee discrimination between the target sequence and other closely related sequences (See page 11.4, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to produce the Rhesus D antigen by constructing an expression vector with the polynucleotide which encodes the Rhesus D antigen as taught by of Westhoff *et al* or Cherif-Zahar *et al* and producing a recombinant host cell using the said expression vector and culturing the host cell under conditions which express the polypeptide in order to recover the polypeptide from the culture as taught by the Sambrook *et al*. It would be been obvious to one having ordinary skill in the art at the time the invention was made to produce oligonucleotide as taught by Sambrook *et al* that would hybridize to the nucleic acid molecule encoding a Rhesus D antigen as taught by Westhoff *et al* or Cherif-Zahar *et al*.

One having ordinary skill in the art at the time the invention was made would have been motivated to produce said polypeptides using recombinant techniques because there would be a higher yield of polypeptide with greater purity as taught by Sambrook *et al*. Sambrook *et al* teach the use oligonucleotides for screening and rapid isolation of cloned copies of large numbers of genes. The recitation of oligonucleotide is 12 to 50 or 15 to 24 nucleotides in length is within the purview of one skill in the art at the time the invention is made as taught by Sambrook *et al*.

Applicants' arguments filed 3/8/02 have been fully considered but are not found persuasive.

Applicants' position is that neither Westhoff *et al* nor Cherif-Zahar *et al* teach or suggest a nucleic acid encoding a Rhesus D antigen and Sambrook et al fails to provide that which is missing from Westhoff *et al* and Cherif-Zahar *et al.*

However, the teachings of Westhoff *et al* and Cherif-Zahar *et al* have been discussed supra. Further, applicants are claiming any nucleic acid sequence encoding a human Rhesus D antigen, not just the specific nucleic acid molecule of SEQ ID NO: 41 having a missense mutation in its transmembrane and/or intracellular regions.

16. Claims 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over Westhoff *et al* (of record, Blood 83: 3098-3100, 1994; PTO 892) or Cherif-Zahar *et al* (of record, Proc. Natl. Sci. U.S.A. 87: 6243-6247, 1990; PTO 892) each in view of Sambrook *et al* (of record, *Molecular Cloning*, 1989, Cold Spring Harbor Laboratory, CSH, NY, Ch. 17) as applied to claims 10-12 and 14 and further in view of US Pat No. 6,200,802 (Filed Oct 1993, PTO 892).

The teachings of Westhoff *et al* (Accession number A46368), Cherif-Zahar *et al* (Accession No. A30405) and Sambrook *et al* have been discussed supra.

The claimed invention in claim 48 differs from the references only by the recitation of a kit comprising the oligonucleotide.

The '802 patent teaches a kit comprising oligonucleotide for screening assays (see column 33, lines 43-50, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to oligonucleotide as taught by the '802 patent with the oligonucleotide as taught by Sambrook *et al* that hybridizes to the polynucleotide as taught by Westhoff *et al*, or Cherif-Zahar *et al* and packing it in a kit for various screening assays as taught by the '802 patent with the expectation that a kit will allow for convenience and commercial expedience. From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidence by the references.

17. Claims 7, 8 and 49 are free of prior art.

18. No claim is allowed.

19. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

21. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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